PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07K 14/715

A1

(11) International Publication Number: **WO 99/50299**

(43) International Publication Date: 7 October 1999 (07.10.99)

(21) International Application Number: PCT/SE99/00501

(22) International Filing Date: 26 March 1999 (26.03.99)

(30) Priority Data:
9801098-6 30 March 1998 (30.03.98) SE

(71) Applicant *(for all designated States except MG US)*: ASTRA PHARMACEUTICALS LTD. [GB/GB]; Home Park, Kings Langley, Herts. WD4 8DH (GB).

(71) Applicant *(for MG only)*: ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: DELANEY, Stephen [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB).

(74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: RECEPTORS

(57) Abstract

The invention provides sequences which are novel splice variants of the chemokine receptor CXCR3, in particular an isolated nucleic acid molecule which comprises one of: a) the sequence set out in Fig. 1 (Seq.I.D.1), or the complementary strand thereof; b) a sequence which hybridises under stringent conditions to a sequence defined in a) above, or c) a sequence which, but for the degeneracy of the genetic code, would hybridise to a DNA sequence defined in a) or b) above and which sequence codes for a polypeptide having the same amino acid sequence as the amino acid sequence which would be encoded by the sequence to which it would be capable of hybridising or a fragment of variant thereof.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

RECEPTORS

The present invention relates to isolated nucleic acids which encode a chemokine receptor protein designated CXCR3b and to the receptor protein encoded by such nucleic acids.

Chemokines are a family of small cytokines that bring about the recruitment of leukocytes during inflammation. Two families of chemokines are termed CC or CXC chemokines based on the spacing of the first two cysteine residues they contain. Most CXC chemokines attract neutrophils, whereas CC chemokines are less selective and can attract monocytes, eosinophils, basophils and T-lymphocytes. All CC and CXC chemokine receptors are seven transmembrane G-protein coupled receptors and most are receptors for a number of chemokines although a number of specific chemokine receptor interactions exist. Such chemokine receptors are therefore an important target for the development of drugs which antagonise these receptors and thereby modulate inflammatory responses. The modulation of inflammatory responses is of therapeutic benefit in many conditions such as rheumatoid arthritis, psoriasis, multiple sclerosis, transplantation , delayed type hypersensitivity reactions, atherosclerosis and restenosis.

Loetscher, M. *et al.* (J. Exp. Med., 184, 963-969 (1996)) describe the cloning of a human CXC receptor for two CXC chemokines (IP10 and Mig) which are secreted by monocytes. This receptor is referred to as either CXCR3 or CXCR3a. Unlike other known chemokine receptors, this receptor is expressed in activated, but not in resting T-lymphocytes. It may therefore play an important role in the selective recruitment of T-cells which occurs in T-cell mediated inflammatory conditions.

The present invention relates to a novel variant of this CXC receptor which is a splice variant resulting in the production of an altered amino terminus. The splice variant has been designated 'CXCR3b' and may have an altered pattern of tissue distribution and of function in the inflammatory process. The receptor is therefore particularly useful for identifying chemokines responsible for mediating inflammatory reactions via interaction

with CXCR3b and for identifying compounds liable to be capable of therapeutic benefit via agonism or antagonism of CXCR3b.

Therefore, according to the present invention, there is provided an isolated nucleic acid molecule which comprises one of :

a) the sequence set out in Fig. 1 (Seq. I.D.1), or the complementary strand thereof,

b) a sequence which hybridises under stringent conditions to a sequence defined in a) above, or

c) a sequence which, but for the degeneracy of the genetic code, would hybridise to a DNA sequence defined in a) or b) above and which sequence codes for a polypeptide having the same amino acid sequence as the amino acid sequence which would be encoded by the sequence to which it would be capable of hybridising or a fragment or variant thereof.

Preferably a DNA sequence of the present invention as described in b) above has the sequence given in Fig. 2 (Seq. I.D.3).

Also included in the scope of the present invention is any isolated RNA molecule capable of being encoded by a DNA molecule of the present invention.

There is also provided an isolated polypeptide which is coded by any of the nucleic acids of the present invention and which preferably has an amino acid sequence comprising the sequence set out in Fig. 3 (Seq. I.D.2) and more preferably has the amino acid sequence of CXCR3b as set out in Fig. 4 (Seq. I.D.4) or a fragment or variant thereof.

A fragment or variant polypeptide of the present invention is one which contains deletions, insertions or alterations in the amino acid sequence but has substantially the same chemokine receptor activity as the polypeptide of which it is a fragment or variant.

There is also provided according to the present invention, nucleic acid vectors comprising a nucleic acid sequence of the present invention; cells containing a nucleic acid or vector of the present invention; purified antibodies reactive with a protein of the present invention; cells expressing an antibody of the present invention; screens for antagonists or agonists of CXCR3b receptor comprising a nucleic acid, vector, protein, antibody or antibody producing cell of the present invention; and ligands capable of agonism or antagonism of a CXC3b receptor function.

Description of Figures:

Fig. 1 shows the DNA sequence of the novel exon of CXCR3b which encodes the amino terminal 14 amino acids of the receptor protein.

Fig. 2 shows the cDNA sequence encoding the CXCR3b receptor protein.

Fig. 3 shows the amino acid sequence of the novel amino terminal sequence of CXCR3b.

Fig. 4 shows the amino acid sequence of the CXCR3b receptor protein.

Nucleic acids and polypeptides of the present invention may be synthesised by known techniques and particularly by the methods described in the Examples hereto.

Nucleic acids of the present invention may be RNA or DNA molecules. A DNA molecule of the present invention may be genomic DNA, a synthetic oligonucleotide or more preferably is cDNA.

DNA sequences of the present invention which are characterised by their ability to hybridise under stringent conditions to sequences described herein may be identified by their ability to hybridise under conditions no less stringent than the following: hybridisation

would be performed at 65°C in 6XSSC (0.9M NaCl, 90mM tri-sodium citrate, pH 7.0), 10X Denhardts solution (0.2% BSA, 0.2% Ficoll, 0.2% polyvinylpyrrolidone) and sonicated salmon sperm DNA at 100ug/ml. Washing would be carried out at 65°C in 6XSSC (0.9M NaCl, 90mM tri-sodium citrate, pH 7.0), 0.1% sodium dodecyl sulphate; or an alternative hybridisation protocol defining the same level of stringency. The hybridisation may suitably be probed with labelled oligonucleotides: 5'-CAGGG CTGGC CCACA GC-3' and/or 5'-AGGGT CACCA CAGGG TTGG-3'.
The probe may be labelled with any suitable label but preferably ^{32}P may be used.
Further details about stringency conditions can be found in Current Protocols in Molecular Biology (Ausubel, F.M. *et al.*, eds., Vol. 1, Suppl. 26, 1991). Preferably, the degree of hybridisation (i.e. the fraction of matched complementary nucleotide pairs) is at least 90%, more preferably at least 95% and most preferably 100%.

Vectors, proteins, antibodies or antibody producing cells of the present invention may also be produced by known techniques and like nucleic acids of the present invention may be produced using techniques described in Sambrook, J., Fritsch, E.F. and Maniatis, T. (1989) Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York.

Proteins of the present invention (which term as used herein is intended to include polypeptides and peptides) are preferably produced recombinantly from a nucleic acid of the present invention but may also be purified proteins isolated from natural sources or may be chemically synthesised.

The terms' polypeptide' and 'protein' are used synonymously herein.

The terms 'isolated DNA', 'isolated RNA' or 'isolated polypeptide' molecules as used herein is taken to mean that the relevant molecule is separated from at least one biological component with which it would normally be associated in nature.

The present invention will now be illustrated by the following Examples which are in no way to be construed as limiting the scope of the present invention. The abbreviation 'PCR' used in the Examples means 'Polymerase Chain Reaction'.

EXAMPLE 1

Cloning of novel CXCR3 splice variants

PCR was performed on DNA prepared from a human lung cDNA library (Clontech QuickScreen). A primer specific for the CXCR3 sequence HPRB1 (5'-AGGAA GGTGT CGGTG CTGCT C-3'), was used in combination with a phage vector (λgt10) specific primer F208 (5'-CCACA GATCT AGCAA GTTCA GCCTG GTTAA G-3'). Amplification was performed with a thermal profile of 94°C for 1 minute, then 35 cycles of 94 °C 30s, 65 °C 30s, 72 °C 1 min using a Taq and Pfu polymerase mix (Amersham). A nested reaction in which F208 was used first with HPR1 for 15 cycles and then with a second CXCR3 specific primer HPR2 (5'-AGCGT GTCTG CTACA GTAGG TG-3') for a further 20 cycles also gave CXCR3b products. PCR products were purified (Promega Wizard PCR prep system) and ligated into the Eco RV site of pZero (Invitrogen). Recombinant plasmids were sequenced and searching of the Genbank database was performed using the GCG package.

EXAMPLE 2

Expression studies

The sites of the expression of the novel CXCR3b splice variant have been investigated. Primers were designed using the novel CXCR3a and b sequence to allow PCR reactions specific for the two variant forms to be carried out. PCR was performed using these primers on cDNA prepared from human tissues. Expression of both forms was detected in human Th1 and Th2 cells and also faintly in spleen. In all tissues analysed there appeared to be co-expression of both CXCR3 splice forms. Primers specific for the two CXCR3 splice variants were designed and used in RT-PCR reactions on cDNA prepared from

T-cells (Maxim Biotechnologies) and from human tissues (Origene). The primer pair SCM57 (5'-AGCCC AGCCA TGGTC CTTGA-3') and SCM59 (5'-CTGTA GAGGG CTGGC AGGAA-3') were used to amplify CXCR3a transcripts while SCM54 (5'-ATCAG GGGAA TGCCA GGGCT-3') and SCM56 (5'-TCGAA GTTCA GGCTG AAGTC-3') were used to specifically amplify CXCR3b transcripts. Amplification was carried out with a thermal profile of 94 °C 30s, 55 °C 30s, 72 °C 30s for 35 cycles using Taq polymerase (Advanced Biotechnologies).

CLAIMS

1. An isolated nucleic acid molecule which comprises one of :

a) the sequence set out in Fig. 1 (Seq. I.D.1), or the complementary strand thereof,

b) a sequence which hybridises under stringent conditions to a sequence defined in a) above, or

c) a sequence which, but for the degeneracy of the genetic code, would hybridise to a DNA sequence defined in a) or b) above and which sequence codes for a polypeptide having the same amino acid sequence as the amino acid sequence which would be encoded by the sequence to which it would be capable of hybridising or a fragment or variant thereof.

2. A nucleic acid molecule according to claim 1, wherein the nucleic acid is DNA.

3. A nucleic acid molecule according to claim 2, wherein the DNA is cDNA.

4. A nucleic acid vector comprising a DNA sequence as claimed in any one of claims 1 to 3.

5. A cell transformed with a vector as claimed in claim 4.

6. An isolated chemokine receptor encoded by a nucleic acid sequence as defined in any one of claims 1 to 3.

7. A method of identifying a ligand of a chemokine receptor as claimed in claim 6 which comprises combining a compound to be tested with a cell expressing the active receptor under conditions suitable for binding of ligand thereto, and detecting or measuring the formation of a complex between the compound and the receptor.

8. A method according to claim 7, wherein the ligand is an antagonist.

FIGURES

GAAAACCCGGGGCATCAGGGGAATGCCAGGGCTGGCCCACAGCCCAGGGTCACCACAGGGTTGG

FIG. 1

GAAAACCCGGGGCATCAGGGGAATGCCAGGGCTGGCCCACAGCCCAGGGTCACCACAGGGTTGGGTGAGTGACCACCAAG

TGCTAAATGACGCCGAGGTTGCCGCCCTCCTGGAGAACTTCAGCTCTTCCTATGACTATGGAGAAAACGAGAGTGACTCGT

GCTGTACCTCCCCGCCCTGCCCACAGGACTTCAGCCTGAACTTCGACCGGGCCTTCCTGCCAGCCCTCTACAGCCTCCTCTT

TCTGCTGGGGCTGCTGGGCAACGGCGCGGTGGCAGCCGTGCTGCTGAGCCGGCGGACAGCCCTGAGCAGCACCGACACCT

TCCTGCTCCACCTAGCTGTAGCAGACACGCTGCTGGTGCTGACACTGCCGCTCTGGGCAGTGGACGCTGCCGTCCAGTGGG

TCTTTGGCTCTGGCCTCTGCAAAGTGGCAGGTGCCCTCTTCAACATCAACTTCTACGCAGGAGCCCTCCTGCTGGCCTGCAT

CAGCTTTGACCGCTACCTGAACATAGTTCATGCCACCCAGCTCTACCGCCGGGGGCCCCCGGCCCGCGTGACCCTCACCTG

CCTGGCTGTCTGGGGGCTCTGCCTGCTTTTCGCCCTCCCAGACTTCATCTTCCTGTCGGCCCACCACGACGAGCGCCTCAAC

GCCACCCACTGCCAATACAACTTCCCACAGGTGGGCCGCACGGCTCTGCGGGTGCTGCAGCTGGTGGCTGGCTTTCTGCTA

CCCCTGCTGGTCATGGCCTACTGCTATGCCCACATCCTGGCCGTGCTGCTGGTTTCCAGGGGCCAGCGGCGCCTGCGGGCC

ATGCGGCTGGTGGTGGTGGTCGTGGTGGCCTTTGCCCTCTGCTGGACCCCCTATCACCTGGTGGTGCTGGTGGACATCCTCA

TGGACCTGGGCGCTTTGGCCCGCAACTGTGGCCGAGAAAGCAGGGTAGACGTGGCCAAGTCGGTCACCTCAGGCCTGGGC

TACATGCACTGCTGCCTCAACCCGCTGCTCTATGCCTTTGTAGGGGTCAAGTTCCGGGAGCGGATGTGGATGCTGCTCTTGC

GCCTGGGCTGCCCCAACCAGAGAGGGCTCCAGAGGCAGCCATCGTCTTCCCGCCGGGATTCATCCTGGTCTGAGA

FIG. 2

MPGLAHSPGSPQGW

FIG. 3

MPGLAHSPGSPQGWVSDHQVLNDAEVAALLENFSSSYDYGENESDSCCTSPPCPQDFSLNFDRAFLPALYSLLFLLGLLGNGAV

AAVLLSRRTALSSTDTFLLHLAVADTLLVLTLPLWAVDAAVQWVFGSGLCKVAGALFNINFYAGALLLACISFDRYLNIVHATQL

YRRGPPARVTLTCLAVWGLCLLFALPDFIFLSAHHDERLNATHCQYNFPQVGRTALRVLQLVAGFLLPLLVMAYCYAHILAVLL

VSRGQRRLRAMRLVVVVVVAFALCWTPYHLVVLVDILMDLGALARNCGRESRVDVAKSVTSGLGYMHCCLNPLLYAFVGVK

FRERMWMLLLRLGCPNQRGLQRQPSSSRRDSSWSETSEASYSGL

FIG. 4

SEQUENCE LISTING

<110> DELANEY, STEPHEN (FOR US ONLY)
ASTRA PHARMACEUTICALS LIMITED
ASTRA AKTIEBOLAG (FOR MG ONLY)

<120> Receptors

<130> F 1943

<140>
<141>

<160> 4

<170> PatentIn Ver. 2.0

<210> 1
<211> 64
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (23)..(64)

<400> 1
gaaaacccgg ggcatcaggg ga atg cca ggg ctg gcc cac agc cca ggg tca 52
Met Pro Gly Leu Ala His Ser Pro Gly Ser
1 5 10

cca cag ggt tgg 64
Pro Gln Gly Trp

<210> 2
<211> 14
<212> PRT
<213> Homo sapiens

<400> 2
Met Pro Gly Leu Ala His Ser Pro Gly Ser Pro Gln Gly Trp
1 5 10

<210> 3
<211> 1159
<212> DNA

<213> Homo sapiens

<220>
<221> CDS
<222> (23)..(1156)

<400> 3

```
gaaaacccgg ggcatcaggg ga atg cca ggg ctg gcc cac agc cca ggg tca  52
                          Met Pro Gly Leu Ala His Ser Pro Gly Ser
                            1               5                  10

cca cag ggt tgg gtg agt gac cac caa gtg cta aat gac gcc gag gtt  100
Pro Gln Gly Trp Val Ser Asp His Gln Val Leu Asn Asp Ala Glu Val
                15                  20                  25

gcc gcc ctc ctg gag aac ttc agc tct tcc tat gac tat gga gaa aac  148
Ala Ala Leu Leu Glu Asn Phe Ser Ser Ser Tyr Asp Tyr Gly Glu Asn
            30                  35                  40

gag agt gac tcg tgc tgt acc tcc ccg ccc tgc cca cag gac ttc agc  196
Glu Ser Asp Ser Cys Cys Thr Ser Pro Pro Cys Pro Gln Asp Phe Ser
        45                  50                  55

ctg aac ttc gac cgg gcc ttc ctg cca gcc ctc tac agc ctc ctc ttt  244
Leu Asn Phe Asp Arg Ala Phe Leu Pro Ala Leu Tyr Ser Leu Leu Phe
    60                  65                  70

ctg ctg ggg ctg ctg ggc aac ggc gcg gtg gca gcc gtg ctg ctg agc  292
Leu Leu Gly Leu Leu Gly Asn Gly Ala Val Ala Ala Val Leu Leu Ser
75                  80                  85                  90

cgg cgg aca gcc ctg agc agc acc gac acc ttc ctg ctc cac cta gct  340
Arg Arg Thr Ala Leu Ser Ser Thr Asp Thr Phe Leu Leu His Leu Ala
                95                  100                 105

gta gca gac acg ctg ctg gtg ctg aca ctg ccg ctc tgg gca gtg gac  388
Val Ala Asp Thr Leu Leu Val Leu Thr Leu Pro Leu Trp Ala Val Asp
            110                 115                 120

gct gcc gtc cag tgg gtc ttt ggc tct ggc ctc tgc aaa gtg gca ggt  436
Ala Ala Val Gln Trp Val Phe Gly Ser Gly Leu Cys Lys Val Ala Gly
        125                 130                 135

gcc ctc ttc aac atc aac ttc tac gca gga gcc ctc ctg ctg gcc tgc  484
Ala Leu Phe Asn Ile Asn Phe Tyr Ala Gly Ala Leu Leu Leu Ala Cys
    140                 145                 150

atc agc ttt gac cgc tac ctg aac ata gtt cat gcc acc cag ctc tac  532
```

```
Ile Ser Phe Asp Arg Tyr Leu Asn Ile Val His Ala Thr Gln Leu Tyr
155                 160                 165                 170

cgc cgg ggg ccc ccg gcc cgc gtg acc ctc acc tgc ctg gct gtc tgg   580
Arg Arg Gly Pro Pro Ala Arg Val Thr Leu Thr Cys Leu Ala Val Trp
                175                 180                 185

ggg ctc tgc ctg ctt ttc gcc ctc cca gac ttc atc ttc ctg tcg gcc   628
Gly Leu Cys Leu Leu Phe Ala Leu Pro Asp Phe Ile Phe Leu Ser Ala
            190                 195                 200

cac cac gac gag cgc ctc aac gcc acc cac tgc caa tac aac ttc cca   676
His His Asp Glu Arg Leu Asn Ala Thr His Cys Gln Tyr Asn Phe Pro
        205                 210                 215

cag gtg ggc cgc acg gct ctg cgg gtg ctg cag ctg gtg gct ggc ttt   724
Gln Val Gly Arg Thr Ala Leu Arg Val Leu Gln Leu Val Ala Gly Phe
    220                 225                 230

ctg cta ccc ctg ctg gtc atg gcc tac tgc tat gcc cac atc ctg gcc   772
Leu Leu Pro Leu Leu Val Met Ala Tyr Cys Tyr Ala His Ile Leu Ala
235                 240                 245                 250

gtg ctg ctg gtt tcc agg ggc cag cgg cgc ctg cgg gcc atg cgg ctg   820
Val Leu Leu Val Ser Arg Gly Gln Arg Arg Leu Arg Ala Met Arg Leu
                255                 260                 265

gtg gtg gtg gtc gtg gtg gcc ttt gcc ctc tgc tgg acc ccc tat cac   868
Val Val Val Val Val Val Ala Phe Ala Leu Cys Trp Thr Pro Tyr His
            270                 275                 280

ctg gtg gtg ctg gtg gac atc ctc atg gac ctg ggc gct ttg gcc cgc   916
Leu Val Val Leu Val Asp Ile Leu Met Asp Leu Gly Ala Leu Ala Arg
        285                 290                 295

aac tgt ggc cga gaa agc agg gta gac gtg gcc aag tcg gtc acc tca   964
Asn Cys Gly Arg Glu Ser Arg Val Asp Val Ala Lys Ser Val Thr Ser
    300                 305                 310

ggc ctg ggc tac atg cac tgc tgc ctc aac ccg ctg ctc tat gcc ttt  1012
Gly Leu Gly Tyr Met His Cys Cys Leu Asn Pro Leu Leu Tyr Ala Phe
315                 320                 325                 330

gta ggg gtc aag ttc cgg gag cgg atg tgg atg ctg ctc ttg cgc ctg  1060
Val Gly Val Lys Phe Arg Glu Arg Met Trp Met Leu Leu Leu Arg Leu
                335                 340                 345

ggc tgc ccc aac cag aga ggg ctc cag agg cag cca tcg tct tcc cgc  1108
```

```
Gly Cys Pro Asn Gln Arg Gly Leu Gln Arg Gln Pro Ser Ser Ser Arg
            350                 355                 360

cgg gat tca tcc tgg tct gag acc tca gag gcc tcc tac tcg ggc ttg   1156
Arg Asp Ser Ser Trp Ser Glu Thr Ser Glu Ala Ser Tyr Ser Gly Leu
        365                 370                 375

tga                                                               1159
```

<210> 4
<211> 378
<212> PRT
<213> Homo sapiens

<400> 4

```
Met Pro Gly Leu Ala His Ser Pro Gly Ser Pro Gln Gly Trp Val Ser
  1               5                  10                  15

Asp His Gln Val Leu Asn Asp Ala Glu Val Ala Ala Leu Leu Glu Asn
             20                  25                  30

Phe Ser Ser Ser Tyr Asp Tyr Gly Glu Asn Glu Ser Asp Ser Cys Cys
         35                  40                  45

Thr Ser Pro Pro Cys Pro Gln Asp Phe Ser Leu Asn Phe Asp Arg Ala
     50                  55                  60

Phe Leu Pro Ala Leu Tyr Ser Leu Leu Phe Leu Leu Gly Leu Leu Gly
 65                  70                  75                  80

Asn Gly Ala Val Ala Ala Val Leu Leu Ser Arg Arg Thr Ala Leu Ser
                 85                  90                  95

Ser Thr Asp Thr Phe Leu Leu His Leu Ala Val Ala Asp Thr Leu Leu
            100                 105                 110

Val Leu Thr Leu Pro Leu Trp Ala Val Asp Ala Ala Val Gln Trp Val
        115                 120                 125

Phe Gly Ser Gly Leu Cys Lys Val Ala Gly Ala Leu Phe Asn Ile Asn
    130                 135                 140

Phe Tyr Ala Gly Ala Leu Leu Leu Ala Cys Ile Ser Phe Asp Arg Tyr
145                 150                 155                 160

Leu Asn Ile Val His Ala Thr Gln Leu Tyr Arg Arg Gly Pro Pro Ala
                165                 170                 175
```

Arg Val Thr Leu Thr Cys Leu Ala Val Trp Gly Leu Cys Leu Leu Phe
180 185 190

Ala Leu Pro Asp Phe Ile Phe Leu Ser Ala His His Asp Glu Arg Leu
195 200 205

Asn Ala Thr His Cys Gln Tyr Asn Phe Pro Gln Val Gly Arg Thr Ala
210 215 220

Leu Arg Val Leu Gln Leu Val Ala Gly Phe Leu Leu Pro Leu Leu Val
225 230 235 240

Met Ala Tyr Cys Tyr Ala His Ile Leu Ala Val Leu Leu Val Ser Arg
245 250 255

Gly Gln Arg Arg Leu Arg Ala Met Arg Leu Val Val Val Val Val Val
260 265 270

Ala Phe Ala Leu Cys Trp Thr Pro Tyr His Leu Val Val Leu Val Asp
275 280 285

Ile Leu Met Asp Leu Gly Ala Leu Ala Arg Asn Cys Gly Arg Glu Ser
290 295 300

Arg Val Asp Val Ala Lys Ser Val Thr Ser Gly Leu Gly Tyr Met His
305 310 315 320

Cys Cys Leu Asn Pro Leu Leu Tyr Ala Phe Val Gly Val Lys Phe Arg
325 330 335

Glu Arg Met Trp Met Leu Leu Leu Arg Leu Gly Cys Pro Asn Gln Arg
340 345 350

Gly Leu Gln Arg Gln Pro Ser Ser Ser Arg Arg Asp Ser Ser Trp Ser
355 360 365

Glu Thr Ser Glu Ala Ser Tyr Ser Gly Leu
370 375

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00501

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07K 14/715
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9725340 A1 (HUMAN GENOME SCIENCE, INC.), 17 July 1997 (17.07.97), see especially the seq. --	1-8
X	WO 9811218 A1 (THEODOR-KOCHER INSTITUTE), 19 March 1998 (19.03.98), see especially page 15, line 34 - page 16, line 5 --	1-8

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 July 1999	14-07-1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Patrick Andersson/Els Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/06/99

International application No.
PCT/SE 99/00501

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9725340 A1	17/07/97	AU 4898496 A	01/08/97
		EP 0886643 A	30/12/98
WO 9811218 A1	19/03/98	AU 4260897 A	02/04/98